**Amendments to the Specification:**

Please replace original paragraph [0006] with the following amended paragraph:

**[0006]** In U.S. Patent no. 6,333,031 and in *Activation of Erythropoietin Receptor Through a Novel Extracellular Binding Site*, Naranda, et al Endocrinology ~~19XX~~ 2002 143(6):2293-2302; *Activation of Erythropoietin Receptor in the Absence of Hormone by a Peptide That Binds to a Domain Different from the Hormone Binding Site*, Naranda, et al., Proc. Natl. Acad. Sci. 1999, 96(13):7569-74 are reported the existence of an extracellular binding site of the EPO receptor ("EPO-R") referred to as the "modulation domain." In the human EPO-R, the modulation domain corresponds to about amino acids 194-216 and has the amino acid sequence QRVEILEGRTECVLSNLRGRTRY (SEQ ID NO:1). Binding of a 23 amino acid peptide having the sequence SEQ ID NO:1 to the EPO-R modulating domain resulted in modulation of the activity of the EPO-R in the presence or absence of the ligand. The peptide, therefore, offers an auxiliary compound for use with EPO to enhance the activity of EPO and reduce the requirement for EPO to achieve analogous activity. The peptide can be readily synthesized efficiently and economically. However, the peptide is small and will be rapidly degraded in the blood. Also, it suffers from the inconvenience of requiring injection.

Please replace original paragraph [0008] with the following amended paragraph:

**[0008]** U.S. Patent no. 6,333,031 and in Activation of Erythropoietin Receptor Through a Novel Extracellular Binding Site, Naranda, et al Endocrinology ~~19XX~~ 2002 143(6):2293-2302; Activation of Erythropoietin Receptor in the Absence of Hormone by a Peptide That Binds to a Domain Different from the Hormone Binding Site, Naranda, et al., Proc. Natl. Acad. Sci. 1999, 96(13):7569-74, describe the modulation domain and SEQ ID NO:1. PCT/US02/064211 describes triazolopyrimidines for use as thrombin inhibitors.

Please replace original paragraph [00061] with the following amended paragraph:

**[00061]** Of the four formulas, the core structure of the triazolopyrimidine is of particular interest. This family of compounds is recognized by having at the 2-position ($(X)_n$-$R_1$), where X is amino, thio or sulfone, n is 0 or 1, where the amino may be unsubstituted or substituted with lower alkyl of from 1 to 3 carbon atoms, and $R_1$ is a lower alkyl group of 1 to 3 carbon atoms, particularly methyl, or an organic group having a six annular membered aromatic group, particularly phenyl or pyridinyl group, preferably phenyl, having from 0 to 3 substituents, where the substituents are halo, particularly chloro, lower alkyl of from 1 to 3 carbon atoms, particularly methyl, nitro, trihalomethyl, particularly trifluoromethyl, and where the phenyl group is terminal and is either directly bonded to the amino or thio atom or bonded through a linking group of from 1 to 4, usually 1 to 3, atoms in the chain, being carbon, nitrogen, or chalcogen, particularly carbon and nitrogen, where heteroatoms are bonded solely to carbon and hydrogen, there being from 0 to 2 heteroatoms in the chain, the linking group generally being a total of from 1 to 8 atoms, usually 1 to 6 atoms other than hydrogen and having from 0 to 2 heterosusbtituents, e.g. oxo, or having α-acetamidinyl having from 0 to 1 N-OH, i.e. N-hydroxy α-acetamidinyl.

Please replace original paragraph [00069] with the following amended paragraph:

**[00069]** Of particular interest are the triazolopyrimidines. More particularly, are those compounds that modulate the activity of the EPO-R, where modulation intends that a detectable signal is transduced into the cell upon binding of the compound, e.g. expression of a protein. Compounds coming within this class are indicated using the designation of the above formula are as follows. These compounds will usually have X as S or NH. $R_1$ will usually be alkyl of from 1 to 3 carbon atoms, particularly $CH_3$, substituted phenyl bonded directly to an annular carbon atom or through a linking group of from 1 to 3 atoms in the chain having from 0 to 3, usually 1 to 2, the atoms being carbon and nitrogen, more particularly methylene and aminoethylene, and the phenyl group being unsubstituted or having substituents that are $CH_3$, Cl, $NO_2$, and $CF_3$,. $R_2$ is $CH_3$, $NH_2$, OH, and aroylamido of from 7 to 8 carbon atoms having from 0 to 2 susbtituents that are $CH_3$, Cl, $NO_2$, and $CF_3$, particularly toluoylamido. $R_3$ is cycloalkylalkyl of from 4 to 8, usually 4 to 6 carbon atoms,

having from 3 to 4 annular atoms, H or carboxy. $R_4$ is H, lower alkyl of from 1 to 3 carbon atoms, particularly $CH_3$, or alkoxymethyl of from 2 to 4 carbon atoms, particularly methoxymethyl. $R_3$ and $R_4$ may be taken together to define phenyl-1,2-dimethylene-α-halo, α-$CH_3$, where the rings may be further susbtituted with from 1-2 substituents that are halo, e.g. F and Cl, $NO_2$, $CH_3$, and $CF_3$. ork, 1987.

Please replace original paragraph [000115] with the following amended paragraph:

**[000115]** The amount of non-peptide EPO-R modulators given to each subject depends on pharmacological properties such as bioavailability, clearance rate and route of administration. The dosage will also depend upon the biological activity of the subject compound, the amount of EPO and/or other drugs being administered, the physiological condition of the host, and the like. Useful dosage ranges will be 0.01 to 200μg/kg, more usually 0.05 to 100 μg/kg. Administration may be weekly or biweekly, or as often as daily, twice daily, more than twice daily, every two days, or less or more frequently, depending on the level of drug administered.

Please replace original paragraph [000128] with the following amended paragraph:

**[000128]** The library of compounds screened was created as a combination of two libraries: compounds were purchased from Maybridge Plc (Cornwall, UK) and Key Organics Ltd (Cornwall, UK). The libraries were received as microtiter plates. From the plates the compounds were diluted to 10 μM final concentration and used in a screen. Positive hits were identified as those compounds that were able to compete out the biotinylated-ERP peptide in its binding to the target site on EPO-R. 80% of competition was use as a cut off criteria for positive binders. Hits were retested in the binding assay to determine their dose-response curves.

Please replace original paragraph [000137] with the following amended paragraph:

**[000137]** The library of compounds screened was created as a combination of two libraries: compounds were purchased from Maybridge Plc (Cornwall, UK) and Key

Organics Ltd (Cornwall, UK). The libraries were received as microtiter plates. From the plates the compounds were diluted to 10 μM final concentration and used in a screen. Positive hits were identified as those compounds that were able to compete out the biotinylated-ERP peptide in its binding to the target site on EPO-R. 80% of competition was use as a cut off criteria for positive binders. Hits were retested in the binding assay to determine their dose-response curves.

Please replace original paragraph [000149] with the following amended paragraph:

**[000149]** UT-7 cells were grown in Minimal Essential Medium Alpha (MEM-α) containing 20% FBS, 1.5g/L $NaHCO_3$, 5ng/ml GM-CSF, and 100U Penicillin/100μg/ml Streptomycin Sulfate ("P/S"), in T150 flasks (60ml/flask) at 37°C, 5% $CO_2$ to a density of no more than 5 x $10^5$ cells/ml. The cells were starved overnight in MEM-α containing 10% FBS, 1.5g/L $NaHCO_3$ and P/S in T150 flasks (60ml/flask) at a density of 5 x $10^5$ cells/ml, in 5% $CO_2$, 37°C. The cells were then centrifuged in a swinging-bucket rotor at 200 x g for 5 minutes at room temperature. The supernatant was removed, and the cells pooled into one 50 ml conical tube. The cells were washed twice with serum-free medium (MEM-α containing 1.5g/L $NaHCO_3$ and P/S). After the last wash, the cells were resuspended to a density of 1 x $10^7$ cells/ml in serum-free medium. The cells were then placed in 15 ml conical tubes in 1 ml aliquots and incubated with the caps loosened for 1 hour at 37°C, 5% $CO_2$. Every 10 minutes, the lower portion of each tube was tapped (flicked) several times to prevent the cells from settling (please note, this step is very important!)

Please replace original paragraph [000152] with the following amended paragraph:

**[000152]** While the cells were starving, GammaBind G Sepharose beads were coated with antibody. To do this, the GammaBind G beads were washed 3 times with PBS (the beads come in a slurry containing 50% beads; 30 μl of this slurry was used per sample). First, the slurry was spun for 15 to 20 seconds, and the supernatant discarded. For each wash, 1 ml ice cold PBS was added to the beads, and the tube inverted several times. The tube was

spun for 15 to 20 seconds, and the supernatant discarded. After the last wash, the supernatant was discarded and 2 µg (10 µl) anti-phosphotyrosine antibody (PY99) per sample was added to the beads. Next, enough PBS was added so that the tube contains 50% beads and 50% liquid (for example, for 10 samples, 300µl slurry was used; this gives approximately 150µl beads). The beads were washed and 100µl antibody plus 50µl PBS were added. The beads were incubated for 2 hours at room temp with end-over-end rotation.

Please replace original paragraph [000153] with the following amended paragraph:

**[000153]** When the cells finished their 1 hour incubation, they were stimulated as follows: The cells receiving the non-peptide EPO-R modulator have a final DMSO concentration of 0.3%. To maintain equivalent conditions for all cells, DMSO was added to all of the cells that do not receive compounds. To obtain a final concentration of 0.3% DMSO, 10µl 30% DMSO was added to 1ml cells and mixed well. 1ml of cells containing 0.3% DMSO was used as a negative control, and 1ml of cells containing 300mU/ml EPO and 0.3% DMSO was used as a positive control.

Please replace original paragraph [000154] with the following amended paragraph:

**[000154]** **Dilutions**: The samples were diluted to 100x their final concentration and 10ml of each dilution was added to 1ml of cells to obtain the final concentration. To obtain a final concentration of 30µM ERP, 30µl of the 1mM stock solution was added directly to 1ml of cells. For the dilutions, see the table below:

| Final Conc. | 100x | Dilutions |
|---|---|---|
| 300mU/ml EPO | 30U/ml | 6µl 500U/ml EPO stock + 94µl ice cold PBS |
| 30µM Compound | 3mM | 9µl 10mM Compound stock + 21µl $H_2O$ |
| 3µM Compound | 0.3mM | 3µl 3mM Compound + 27µl 27% DMSO |

| | | |
|---|---|---|
| 0.3μM Compound | 0.03mM | 4μl 0.3mM Compound + 36μl 27% DMSO |
| 30μM EPO-R | ---- | Add 30μl 1mM EPO-R stock directly to 1ml cells |
| 3μM EPO-R | 0.3mM | 6μl 1mM EPO-R stock + 14μl ice cold $H_2O$ |
| 0.3μM EPO-R | 0.03mM | 3μl 0.3mM EPO-R (above) + 27μl ice cold $H_2O$ |

Please replace original paragraph [000155] with the following amended paragraph:

**[000155]** The samples were incubated for 30 minutes at 37°C, 5% $CO_2$, and every 10 minutes, the samples were mixed by tapping (flicking) the lower portion of each tube several times. The assays were stopped by adding 14ml of ice cold PBS to each sample. The samples were centrifuged at 400 x g, 4°C for 5 minutes in a swinging bucket rotor. The samples were placed on ice, and the supernatant was aspirated. To lyse the cells, 800μl 2x lysis buffer (containing 2x protease inhibitors, added just before use) was added to each cell pellet and pipeted up and down several times. The cells were then incubated on ice for 30 minutes. The samples were transferred into 1.5 ml microcentrifuge tubes, and spun for 10 minutes at 10,000 x g, 4°C. While the samples were spinning, the antibody-coated GammaBind G beads were separated into equivalent aliquots in an appropriate number of 1.5ml microcentrifuge tubes. The supernatant was taken from each sample, and added to the anti-phosphotyrosine-coated GammaBind G beads, and the beads and supernatant mixture were incubated with end-over-end rotation over night at 4°C. The samples were spun for 15 to 20 seconds, and the supernatant was discarded. The beads were washed twice with 800μl 1x lysis buffer (containing 1x protease inhibitors, added just before use) and once with 800μl of a 1:1 mix of lysis buffer: 125mM Tris pH 6.8 (for each wash, add buffer, invert the tube several times, spin for 15 to 20 seconds, and discard the supernatant). 45 μl 1x sample buffer was added to each sample. The samples were heated for 5 minutes at 95°C, centrifuged briefly (approx. 20 seconds) and examined by SDS-PAGE.

Please replace original paragraph [000156] with the following amended paragraph:

**[00156]** The samples were run on two 8% SDS-Polyacrylamide gels under reducing conditions. The procedure was to transfer the proteins to Immobilon-P membranes (transfer for 60min., at 300mA, in 10mM CAPS transfer buffer, pH 11 containing 10% MeOH); block the membranes in blotto for 1 hr at room temp; incubate one membrane with α-STAT 5b antibody, and the other with α -EPO-R antibody (dilute both antibodies 1:1,000 in blotto) at 4°C overnight; wash the membranes 3 times in blotto at room temp., 4 minutes per wash; add α -Rabbit-AP secondary antibody diluted 1:2,000 in blotto to both membranes; incubate for 2 hours at room temp; wash the membranes 3 times with blotto, 4 minutes per wash; wash the membranes twice with 1x TST, 4 minutes per wash; wash the membranes once with 1x TSM, 4 minutes per wash; add 10ml BCIP/NBT substrate to each membrane for detection.

Please replace original paragraph [000158] with the following amended paragraph:

**[000158]** 100x Protease Inhibitors:

| | |
|---|---|
| 1mg/ml Aprotinin | 20mg Aprotinin |
| 100µg/ml Pepstatin A* | 2mg Pepstatin A* |
| 100µg/ml Leupeptin | 2mg Leupeptin |
| 100µg/ml Chymostatin* | 2mg Chymostatin* |
| 23.8mg/ml AEBSF | 476mg AEBSF |

*Dissolve Chymostatin and Pepstatin-A in 100µl DMSO before combining with the other inhibitors. Bring volume up to 20ml in $H_2O$. Add to Lysis Buffer just before using.

Please replace original paragraph [000159] with the following amended paragraph:

**[000159]** Sample Buffer:

100µl 50% Glycerol,
0.05% Bromphenol Blue
20µl β-Mercaptoethanol
40µl 10% SDS
160µl 1x gel running buffer (electrophoresis buffer)

Please replace original paragraph [000164] with the following amended paragraph:

**[000164] BCIP/NBT Substrate:**

NBT stock: 50mg/ml in 70% Dimethyl Formamide. Store at –20°C; BCIP stock: 50mg/ml in 100% Dimethyl Formamide. Store at –20°C; Just before using, combine 10ml 1x TSM with 66µl 50mg/ml NBT, and 33µl 50mg/ml BCIP; Mix well, and apply to filter.

Please replace original paragraph [000169] with the following amended paragraph:

**[000169]** Bone marrow cells were isolated from mouse femurs. Cells were washed twice with PBS and resuspended to a density of $6.5 \times 10^6$ cells/ml in media. 300 µl ($6.5 \times 10^5$ /ml) of cells were mixed with 1.5 ml of methylcellulose media (Stemcell Technology) to which the desired concentration of compound or the EPO was added. The mixture was poured onto 35 mm dishes; all the conditions are performed in duplicates. The incubation was for eight days at 37°C, 5% $CO_2$. The colonies were scored on day seven.

Please replace original paragraph [000182] with the following amended paragraph:

**[000182]** 11 nmole/kg/mouse/day x 0.025 kg x 12 mice = 3.3 nmoles/day; Injections are delivered i.p. in a volume of 0.5 cc/mouse/day = 0.5cc/mouse/day x 12 mice = 6 cc/day; non-peptide EPO-R binding small molecule for 20 mice: 3.3 nmoles/6 cc each day: 3.85 nmole/7 cc each day; non-peptide EPO-R binding small molecule aliquot at 2 mM = 2 nmole/µL; 3.85 nmole per day in 7 cc (0.55 nmole/mL); Therefore: 3.85 nmole divided by 2 nmole/µL stock = 1.925 µL at 2mM; Prepare in advance at least 10 aliquots of non-peptide EPO-R binding small molecule at 2mM in small microfuge tubes, each with a volume of 2 µL. Freeze these aliquots; On each day of injections, add 1 thawed aliquot of the non-peptide EPO-R binding small molecule at 2mM containing a 2 µL volume to a tube containing 7 cc of sterile saline (0.1 mg/mL BSA). This results in an non-peptide EPO-R binding small molecule injection solution with 0.55 nmole/mL concentration.

Please replace original paragraph [000183] with the following amended paragraph:

**[000183] Erythropoietin Dose at 1.5 μg/kg/day:** Calculations for daily injections given to 12 male mice (8 wks old~25 g) over a period of 10 days: 1.5 μg/kg/mouse/day x 0.025 kg x 12 mice = 0.45 μg/day; Injections are delivered i.p. in a volume of 0.5 cc/mouse/day = 0.5cc/mouse/day x 12 mice = 6 cc/day; EPO for 12 mice: 0.45 μg/ 6 cc each day: 0.525 μg/ 7 cc each day; Reconstitute 500 units (5 μg) of EPO (#287-TC-500, R&D Systems) with 1 mL PBS to provide a stock concentration at 5 μg/mL; Use 0.525 μg per day in 7 cc (75 ng/mL); Therefore: 0.525 μg divided by 5 μg/mL stock = 0.105 mL at 5 μg/mL ~100 μL at 5 μg/mL; Prepare in advance at least 10 aliquots of EPO at 5 μg/mL in small microfuge tubes, each with a volume of 100 μL. Freeze these aliquots; On each day of injections, add 1 thawed aliquot of the EPO at 5 μg/mL with a volume of 100 μL to a tube containing 7 cc of sterile saline (0.1 mg/mL BSA). This results in an erythropoietin injection solution with a concentration of 75 ng/mL.

Please replace original paragraph [000186] with the following amended paragraph:

**[000186] Carboplatin + Erythropoietin (1.5 μg/kg/day) Positive Control Group:** Each animal is given a 0.5 cc i.p. injection of carboplatin at 6 mg/mL on day 0. Each animal is given a 0.5 cc i.p. injection of Erythorpoietin at 75 ng/mL on days 1 through 10.

Please replace original paragraph [000193] with the following amended paragraph:

**[000193]** Primary cultured cells were used as a model to evaluate the subject small molecule effect on CNS. Glutamate neurotoxicity can be most directly studied using neurons prepared from the brain at the late embryonic stage and subsequently cultured for maturation. To examine the effect of the subject small molecules (E5A24 and E5A29) on glutamate-induced neuronal death, cortical neurons isolated from embryonic day 18 rats, were cultured for 10 days. Subsequently, neurons were treated for 24 hours with or without the subject small molecules, and further exposed to 300 μM glutamate for 24 hours. After glutamate was washed out, the cells were cultured for another 24 hours. During the glutamate challenge and subsequent culture, the subject small molecules were absent.

Finally, the cell viability was examined. Figure 16 shows that subject small molecules will increase cell survival by 60%. Thus, small molecules prevented glutamate induced neuronal death in a dose–responsive manner. Experiments were performed according to the literature (Morishita *et. al.,* Neuroscience 76, 105, 1997).